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PII: S0040-4020(19)30335-7

DOI: https://doi.org/10.1016/j.tet.2019.03.038

Reference: TET 30224

To appear in: *Tetrahedron*

Received Date: 3 February 2019

Revised Date: 19 March 2019

Accepted Date: 22 March 2019

Please cite this article as: Dong W, Xu G, Tang W, Enantioselective palladium-catalyzed C(sp^2)-H carbamoylation, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.03.038.

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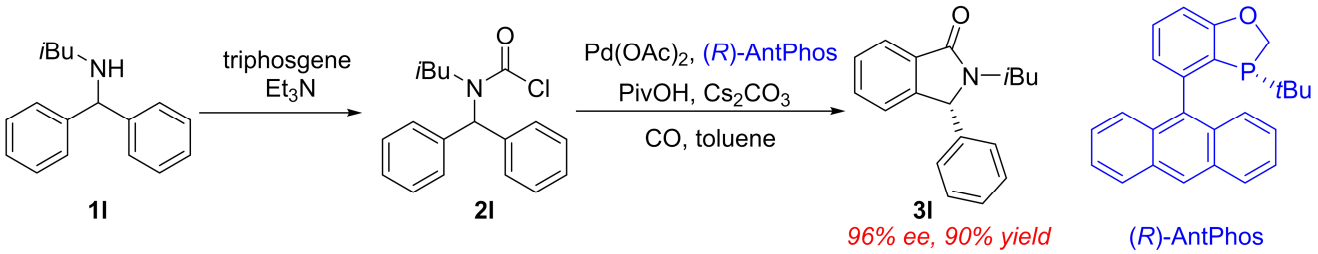

1l 2l 3l

96% ee, 90% yield

(*R*)-AntPhos

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Carbamoylation
Enantioselective
isoindolines
Palladium catalysis
Chiral phosphorus ligand

ABSTRACT

An enantioselective palladium-catalyzed C(sp^2)-H carbamoylation for the preparation of chiral isoindolines was described for the first time. With chiral monophosphorus ligand (*R*)-AntPhos as the ligand, a series of chiral isoindolines were prepared from diarylmethyl carbamoyl chlorides in excellent yields and enantioselectivities with the palladium loading as low as 1 mol%. Initial mechanistic studies indicated the asymmetric cyclization catalyzed a palladium species with a single chiral monophosphorus ligand.

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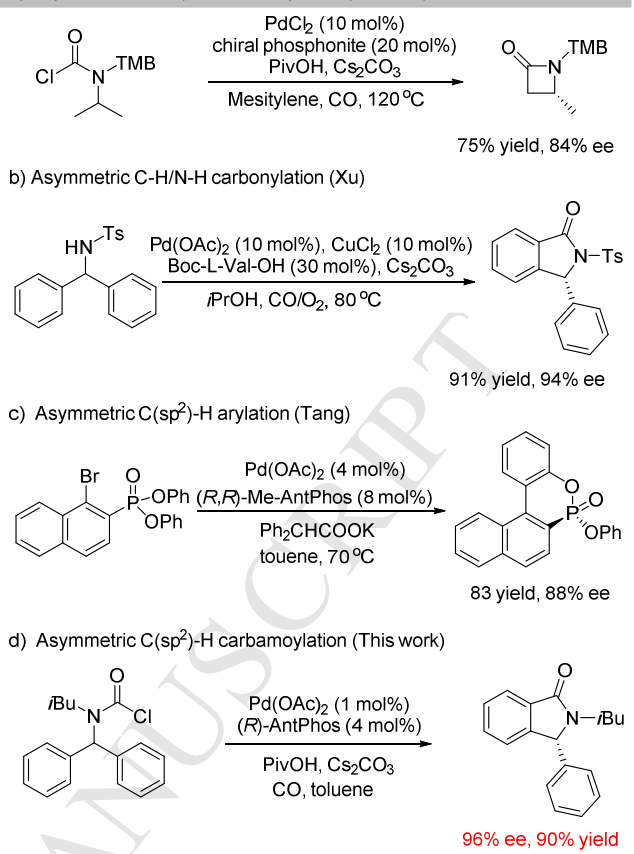
1. Introduction

Enantioselective palladium-catalyzed carbon-carbon bond-forming reaction has become one of most important asymmetric transformations in organic synthesis and has shown increasing applications. Asymmetric cyclization using simple and easily accessible starting materials such as unfunctionalized arenes to build chiral building blocks or intermediates has become an attractive method. In particular, the recent advances in palladium-catalyzed asymmetric C(sp^2)-H and C(sp^3)-H arylation from aryl halides has received considerable attention.[1] The palladium-catalyzed carbamoylation using carbamoyl chlorides as the starting materials is an attractive method to make amides or lactams. Baudoin and co-workers[2] have recently developed a C(sp^3)-H carbamoylation to form a range of β-lactams (Scheme 1a). With a chiral TADDOL-derived phosphonite as the ligand, an enantioselective version was achieved to provide the chiral lactam product in 84% ee. However, to the best of our knowledge, no asymmetric C(sp^2)-H carbamoylation has ever been reported.

Isoindolines are important structural units in numerous natural products and bioactive compounds.[3] Synthesis of chiral isoindolines has gained considerable attention[4]. Xu and co-workers[5] have recently reported an interesting enantioselective C-H carbonylation of sulphonamides with Pd/Cu co-catalysts (Scheme 1b). With a chiral mono-*N*-protected amino acid as the ligand, excellent enantioselectivities (up to 96% ee's) were achieved on a series of lactam products, albeit with the requirement of 10 mol% catalyst loading. We reported an asymmetric intramolecular Pd-catalyzed C(sp^2)-H arylation of diaryl *ortho*-bromo aryl phosphonates by employing a P-chiral monophosphorus ligand.[6,7] With (*R*, *R*)-Me-AntPhos as the ligand, a series of P-chiral biaryl phosphonates were synthesized in high yields (up to 92%) and good enantioselectivities (up to 88% ee) under mild conditions (Scheme 1c). We proposed that a similar asymmetric cyclization could also be developed on carbamoyl chlorides as the substrates for preparation of chiral lactams. Herein we report a highly enantioselective palladium-catalyzed C(sp^2)-H carbamoylation of diarylmethyl carbamoyl chlorides by employing AntPhos as the chiral ligand, providing a series of chiral isoindolines in excellent yields and enantioselectivities with the palladium loading as low as 1 mol% (Scheme 1d).

2. Result and discussion

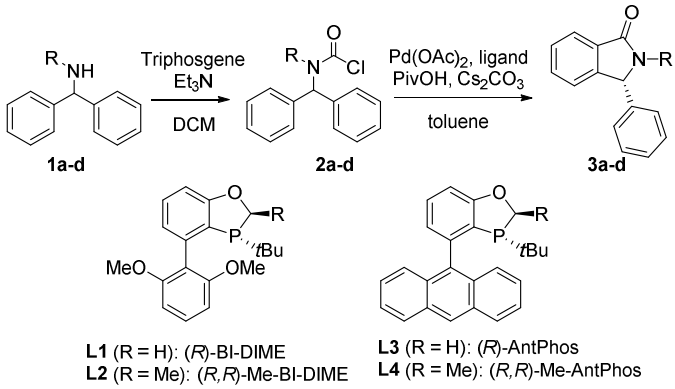
The preparation of carbamoyl chlorides **2a-d** was accomplished from corresponding secondary amines **1a-d** by treatment with triphosgene and NEt_3 in DCM. After a simple aqueous work-up, the crude carbamoyl chlorides **2a-d** were used directly without further purifications for the study of enantioselective palladium-catalyzed cyclization.



Scheme 1. Asymmetric C(sp^2)-H carbamoylation reaction

We initially chose carbamoyl chloride **2a** as the substrate for study (Table 1 entries 1-4). The reactions were carried out in toluene at 80 °C for 24 h with cesium carbonate as the base and PivOH as the additive in the presence of $Pd(OAc)_2$ (5 mol %) and a chiral monophosphorus ligand (5 mol %). To our delight, the four monophosphorus ligands **L1-4** developed in our group all provided the cyclization product **3a** in high yields, however with no or low enantioselectivities. Among them, (*R*)-AntPhos (**L3**) provided a 37% ee. We thought the *N*-R substituent might play a significant influence on the enantioselectivity, hence carbamoyl chlorides **2b-d** with different *N*-R substituents were prepared from corresponding amines **1b-d** and cyclization of **2b-d** under palladium catalysis with **L3** as the ligand were tested (entries 5-7). Both substrates **2b-c** led to their corresponding cyclization products with moderate yields and low ees, while the *N*-phenyl substrate **2d** was inactive. Product **3c** was obtained in 45% ee (entry 6). The main side-reaction during the transformation was the decarbonylation to form the secondary amine **1b-d**.[1t-v] Since change of the *N*-substitution did not provide a pronounced effect on enantioselectivity, we decided to change the Pd/**L3** ratio of the reaction. Thus, the amount of ligand **L3** was changed from 5 mol % to 10, 15, 20 mol % with **2b** as the substrate (entries 8-12). Surprisingly, when 10 mol % of **L3** was employed, the ee value of **3b** increased to 91% (entry 8). Further increase of the ligand loading not only enhanced the enantioselectivity but also the yield of **3b**. When 5 mol % $Pd(OAc)_2$ and 20 mol % of **L3** were employed in this reaction, a 96% ee and 80% isolated yield were achieved (entry 10). A lower reaction temperature (70 °C) was also applicable, albeit with slightly less ee and yield (entry 11). Despite the excellent enantioselectivity and good yield, we were not satisfied with

Table 1. Enantioselective C(sp^2)-H carbamoylation: optimization of reaction conditions

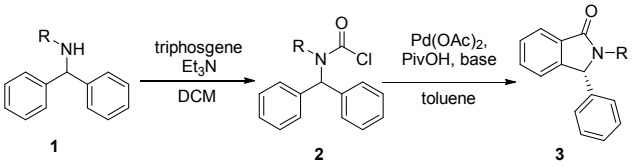


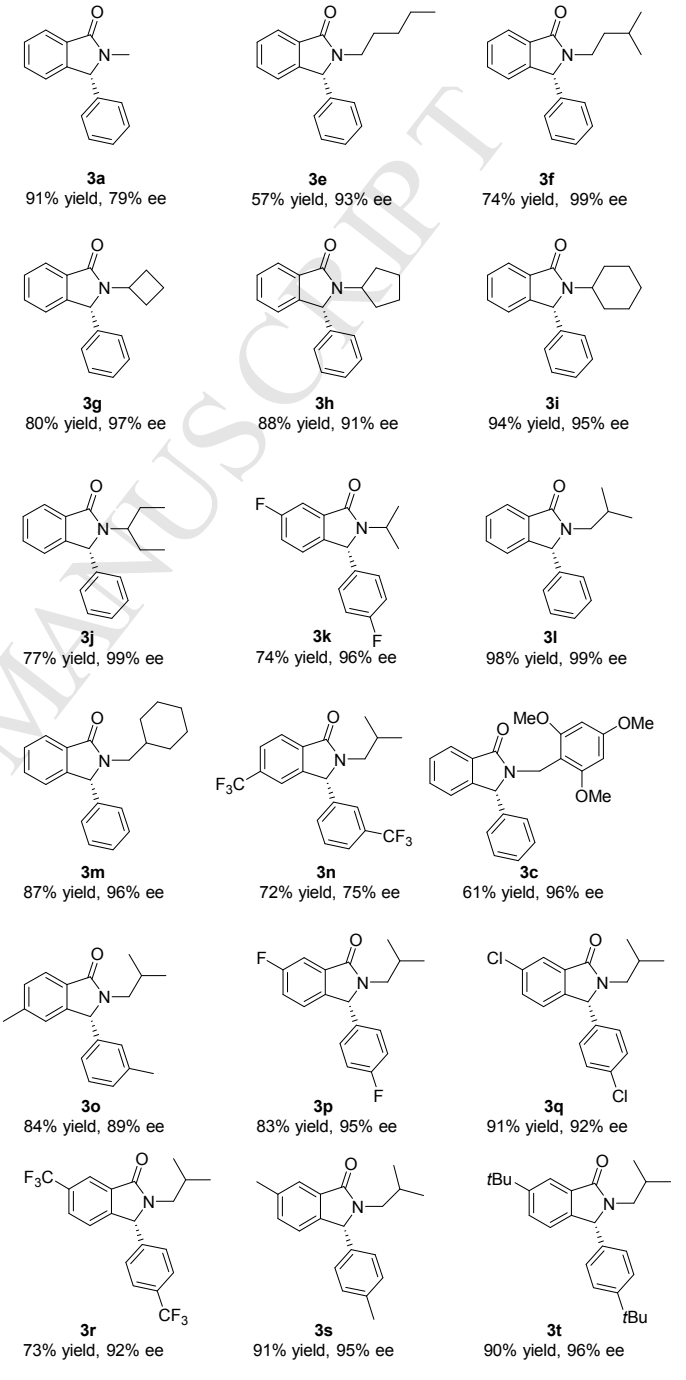
Entries[a]	R	L*	CO (atm)	Pd/L* (mol%)	T (°C)	Yield (%)[b]	Ee%[c]
1	Me (**3a**)	**L1**	-	5/5	80	75	0
2	Me (**3a**)	**L2**	-	5/5	80	85	0
3	Me (**3a**)	**L3**	-	5/5	80	90	37
4	Me (**3a**)	**L4**	-	5/5	80	93	0
5	*i*Pr (**3b**)	**L3**	-	5/5	80	57	30
6	(2',4',6'-(MeO)$_3$Bn (**3c**)	**L3**	-	5/5	80	61	45
7	Ph (**3d**)	**L3**	-	5/5	80	0	nd
8	*i*Pr (**3b**)	**L3**	-	5/10	80	69	91
9	*i*Pr (**3b**)	**L3**	-	5/15	80	75	94
10[f]	*i*Pr (**3b**)	**L3**	-	5/20	80	80	96
11[e]	*i*Pr (**3b**)	**L3**	-	5/20	70	72	90
12	*i*Pr (**3b**)	**L3**	-	1/4	80	41	75
13	*i*Pr (**3b**)	**L3**	3	1/4	80	42	94
14	*i*Pr (**3b**)	**L3**	3	1/3	80	46	87
15	*i*Pr (**3b**)	**L3**	3	1/2	80	17	79
16	*i*Pr (**3b**)	**L3**	3	1/1	80	trace	n.d
17	*i*Pr (**3b**)	**L3**	6	1/4	80	85	92
18	*i*Pr (**3b**)	**L3**	9	1/4	80	**90**	**94**
19	*i*Pr (**3b**)	**L3**	12	1/4	80	92	92

[a] Unless otherwise specified, the reactions were performed at the designated reaction temperature in toluene (1 mL) with **2** (0.1 mmol), Cs_2CO_3 (1.0 equiv), and PivOH (30 mol %) under nitrogen or CO atmosphere for 24 h in the presence of $Pd(OAc)_2$ as the palladium precursor and **L*** as the chiral ligand. The absolute configurations of **3a-c** were assigned by analogy or by comparing the sign of their optical rotation with reported data.[10] [b] Isolated yield. [c] Ee values were determined by chiral HPLC on a chiralpak AD-H column.

the high palladium and ligand loading. Considering the dramatic effect on both ee's and yields with ligand loading, we wondered whether the Pd/**L3** ratio played a major effect. Thus, the reaction was performed in the presence of 1 mol % $Pd(OAc)_2$ and 4 mol % of **L3**, significant decreases on both ee and yield was observed (entry 12). However, the ee was not as low as in entry 5, indicating the ee could be achieved at high level even at 1 mol % palladium loading. Since decarbonylation could be the major side-reaction, we thought weather we could run the reaction under CO[8] atmosphere to inhibit the decarbonylation. Under 3 atm of CO, we were surprised that the ee significantly increased to 94% ee, albeit with a similar yield (entry 13). Decrease of the **L3**/Pd ratio from 4**,** to 3, 2, 1 deteriorated both the yield and the ee (entries 14-16). We thus kept the ratio of **L3**/Pd as 4 and further

Table 2. Enantioselective C(sp^2)-H carbamoylation: substrate scope [a]





[a] Unless otherwise specified, the reactions were performed at 80 °C under CO (9 atm) for 24 h in toluene (2 mL) with **2** (0.2 mmol), $Pd(OAc)_2$ (1 mol %), **L3** (4 mol %), Cs_2CO_3 (0.2 mmol), and PivOH (30 mol %); isolated yields; ee values were determined by chiral HPLC. The absolute configurations by comparing the sign of their optical rotation with reported data.[9]

increased the CO pressure of the reaction. Pleasingly, the yield dramatically increased under 6 atm of CO, indicating the effective inhibition of decarbonylation (entry 17). An excellent ee (94%) and yield (90%) were achieved under 9 atm of CO at 1 mol % palladium loading (entry 18). Further increase of CO did not provide much improved results (entry 19). We thus chose $Pd(OAc)_2$ (1 mol %), (*R*)-AntPhos (4 mol %), Cs_2CO_3 (1 equiv), PivOH (30 mol %), CO (9 atm), toluene as the solvent, and 80 °C as the optimized reaction conditions for further studies.

The substrate scope of this enantioselective palladium-catalyzed C(sp^2)-H carbamoylation was studied under the optimized reaction conditions. Carbamoyl chlorides **2a-t** with various *N*-alkyl substituents were subjected for the cyclization and all provided chiral products in satisfactory yields and good to excellent ee's (Table 2). The *N*-methyl product **3a** was obtained in 79% ee. The relative low ee compared to that of **3b** is possibly due to the smaller size of the methyl group. Products **3e-m** with either primary alkyl groups such as *n*-pentyl, isopentyl, isobutyl, and cyclohexylmethyl, or secondary cyclic and acyclic alkyl groups such as cyclobutyl, cyclopentyl, cyclohexyl, 3-pentyl and isopropyl, all provided excellent ee's and yields. Under the optimized conditions, the *N*-(2',4',6'-$(MeO)_3$Bn product **3c** was also obtained in 96% ee. Various *para*-substituted diarylmethyl carbamoyl chlorides could also be employed. Substituents such as fluoro (**3p**), chloro (**3q**), trifluoromethyl (**3r**), methyl (**3s**), and *tert*-butyl (**3t**) were all compatible. Interestingly, asymmetric cyclization of both *meta*-substituted diarylmethyl carbamoyl chlorides **2n** and **2o** occurred exclusively at the para position to the substituents, forming **3n** and **3o** in good enantioselectivities, respectively. Apparently, much steric hindrance would encounter if the cyclizations occur at the *ortho* positions to the substituents.

The high enantioselectivity achieved at **L3**/Pd ratio of 4 deserved further elaboration. Cyclization of **2l** with a scalemic composition of AntPhos showed a good linear relationship of ee's between the ligand and **3a** (Figure 1), indicating the reaction catalyzed by a palladium catalyst with a single AntPhos ligand. Thus, we speculated that the role of the excess ligand in the transformation was to inhibit background or non-enanatioselective side-reaction. In particular, the secondary amine derived from decarbonylation could play a role for the enantiomeric loss. Under CO atmosphere, the decarbonylation was effectively inhibited and a low palladium loading of 1 mol % was successfully achieved.

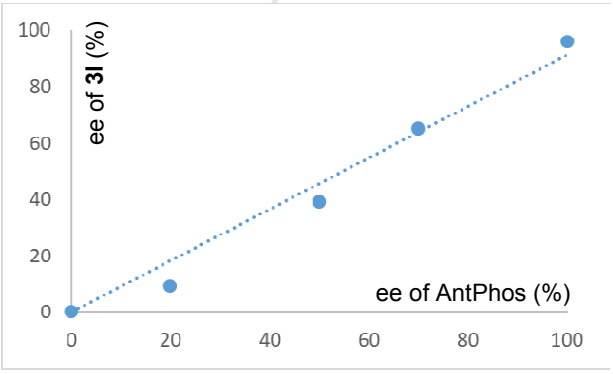


Figure 1. A linear relationship of ees between ligand AntPhos and product **3l**

A brief mechanistic pathway of the C(sp^2)-H carbamoylation is proposed, as shown in Figure 2. Oxidative addition of carbamoyl chloride **2l** by a Pd (0) species **A** leads to the formation of a Pd(II) species **B**. Under CO atmosphere, the α-elimination of **B** to **E** could be effective inhibited. Under basic conditions, **B** undergoes C(sp^2)-H activation through a concerted metalation-deprotonation pathway,[10] via transition state **C**, to form the palladacyle **D**. Reductive elimination of **D** leads to the formation of product **3l** and regenerates the Pd(0) species **A**. The transition state **C** could have two possible conformers shown in Figure 2. In conformer **b**, a steric interaction between the anthryl group of the ligand and one phenyl substituent of the substrate is much likely, while the more stable conformer **a** leads to product **3l** with the observed stereochemistry.

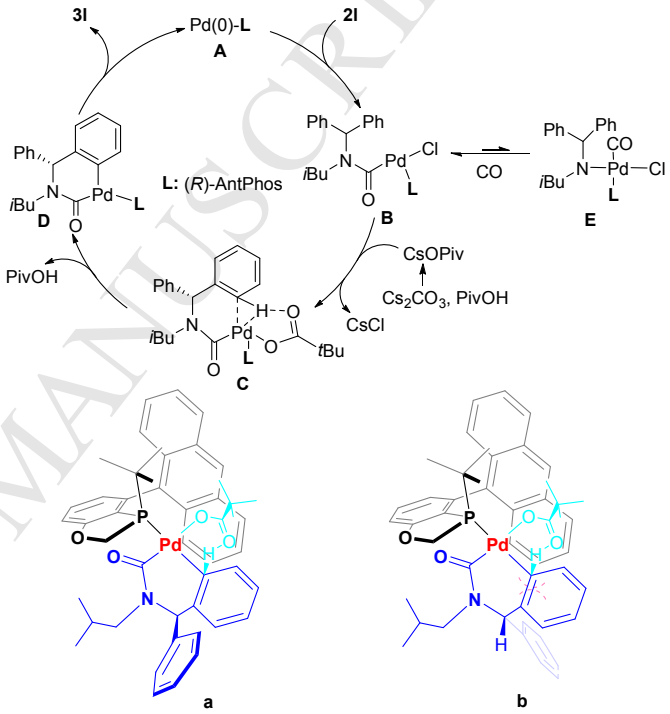
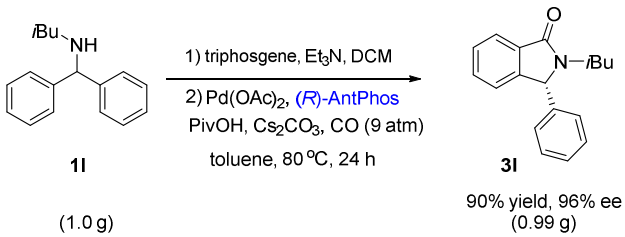


Figure 2. Mechanistic consideration

To demonstrate the practicality of this asymmetric cyclization, the synthesis of **3l** was carried out at a gram scale (Scheme 2). Thus, amine **1l** was transformed to **2l** by treatment of triphosgene and triethylamine in dichloromethane. After aquesous workup, the crude **2l** was subjected for the asymmetric palladium-catalyzed carbamoylation under the optimized reaction conditions and the desired product **3l** was isolated in 90% yield (0.99 g) and 96% ee.



Scheme 2. Gram-scale preparation of **3l**

3. Conclusion

In summary, we have described an enantioselective palladium-catalyzed C(sp^2)-H carbamoylation. With chiral monophosphorus ligand (*R*)-AntPhos as the ligand, a series of chiral isoindolines were prepared from diarylmethyl carbamoyl chlorides in excellent yields and enantioselectivities with the palladium loading as low as 1 mol %. Mechanistic studies indicated the asymmetric cyclization catalyzed a palladium species with a single chiral monophosphorus ligand. This practical method has provided a facile and valuable avenue for preparing chiral lactams in particular chiral isoindoline products for medicinal chemistry.

4. Experimental section

4.1 General procedures

NMR spectra and data were recorded on a Bruker DRX 500 NMR Spectrometer with $CDCl_3$, DMSO-D_6 or CD_3OD as the solvent. 13C chemical shifts were acquired with 1H decoupling. MS data were measured on an Agilent 1100 Series LC/MSD mass spectrometer. Column chromatography was performed with silica gel.

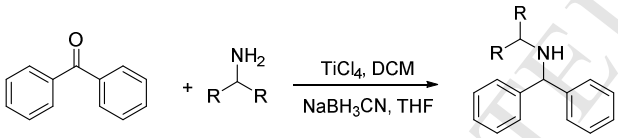
All reagents were used as received from commercial sources unless otherwise specified or prepared as described in the literature. All reagents were weighed and handled in air and refilled with an inert atmosphere of nitrogen an inert atmosphere of nitrogen except for special description in the experimental procedure.

4.2 Synthetic procedures of ligand

P-Chiral monophosphorus ligands were prepared according to procedures described in our previous reports.[11,7b,7d]

4.3 Synthesis procedures of secondary amines

4.3.1 General procedure



Substrates **1a-b, 1e-t** was prepared as follows: To a solution of benzophenone (1.5 g, 8.23 mmol) in DCM (40 mL) was charged secondary amine (2.0 equiv) followed by slow addition of $TiCl_4$ (1.2 mL, 1.2 equiv) at 0 ^oC. The resulting mixture was stirred at rt for 8 h followed by the addition of $NaBH_3CN$ (600 mg in 10 mL THF). The mixture was stirred for additional 4 hours before addition of aqueous NaOH solution (20% w/w, 100 mL) to quench the reaction. The organic layer was separated and the aqueous phase was extracted with DCM. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give product.

Compound **1a**: 95% yield; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ7.41 (d, *J*=8.0 Hz, 4H), 7.32 (m, *J* = 7.0 Hz, 4H), 7.23 (d, *J* = 6.5 Hz, 2H), 4.72 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.93, 128.46, 127.26, 126.98, 69.58, 35.12; HR-MS (ESI): Calculated for $C_{14}H_{15}N$ [M+H]: 198.1276 Found: 198.1277

Compound **1b**: 95% yield; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 4H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.23 (t, *J* = 7.5 Hz, 2H), 5.01 (s, 1H), 1.10-1.14 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.61, 128.42, 127.39, 126.84, 64.29, 46.12, 23.23; HR-MS (ESI): Calculated for $C_{16}H_{19}N$ [M+H]: 226.1589 Found: 226.1590.

Compound **1e**: 90% yield; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42(d, *J* = 7.5 Hz, 4H), 7.31 (t, *J* = 7.5Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 4.84 (s, 1H) 2.59 (t, *J* = 7.0 Hz, 2H), 1.55(m, 2H), 1.31(m, 4H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.18, 128.43, 127.29, 126.92, 67.60, 48.28, 29.84, 29.54, 22.61, 14.05; HR-MS (ESI): Calculated for $C_{19}H_{23}N$ [M+H]: 254.1903, Found 254.1903

Compound **1f**: 88% yield (1.88 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41(d, *J* = 8.5 Hz, 4H), 7.30 (t, *J* = 8.5 Hz, 4H), 7.21(t, *J* = 7.5 Hz, 2H), 4.82 (s, 1H), 2.10 (t, *J* = 7.5 Hz, 2H), 1.66 (m, 1H), 2.10 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.39, 128.41, 127.25, 126.87, 67.77, 46.46, 39.40, 26.04, 22.70; HR-MS (ESI): Calculated for $C_{18}H_{24}N$ [M+H]: 254.1902, Found: 254.1903

Compound **1g**: 54% yield (1.05 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 4H), 7.31(t, *J* = 7.5 Hz, 4H), 7.23 (t, *J* = 7.5 Hz, 2H), 4.85 (s, 1H), 3.2 (m, 1H), 2.20 (m, 2H), 1.63-1.80 (m, 3H), 1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.81, 128.45, 127.35, 127.02, 64.48, 52.07, 31.37, 14.71; HR-MS (ESI): Calculated for $C_{17}H_{20}N$ [M+H]: 238.1590, Found: 238.1590

Compound **1h**: 80% yield (1.65 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 2H), 4.95 (s, 1H), 3.0-3.1 (m, 1H), 1.85-1.92 (m, 2H), 1.67-1.76 (m, 2H), 1.38-1.58 (m, 4H); ^{13}C NMR (125 MHz， $CDCl_3$) δ 144.33, 128.43, 127.47, 126.91, 65.73, 57.66, 33.19, 23.87; HR-MS (ESI): Calculated for $C_{18}H_{22}N$ [M+H]: 252.1746, Found: 252.1747

Compound **1i**: 93% yield (2.03 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 5.07 (s, 1H), 2.39-2.50 (m, 1H), 1.95-2.03 (d, 2H), 1.67-1.77 (m, 2H), 1.59 (m, 1H), 1.08-1.26 (m, 5H); ^{13}C NMR (125 MHz， $CDCl_3$) δ 144.78, 128.39, 127.40, 126.79, 63.66, 53.96, 33.94, 26.24, 25.12; HR-MS (ESI): Calculated for $C_{19}H_{24}N$ [M+H]: 266.1902, Found: 266.1903

Compound **1j**: 85% yield (1.77 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.23 (t, *J* = 7.5 Hz, 2H), 4.99 (s, 1H); 2.42 (m, 1H), 1.49 (m, 4H), 0.91 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.82, 128.36, 127.49, 126.81, 63.97, 56.42, 25.68, 9.67; HR-MS (ESI): Calculated for $C_{18}H_{24}N$ [M+H]: 254.1903, Found: 254.1903.

Compound **1k**: 87% yield (1.87 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.5, 2.5 Hz, 4H) 6.99 (t, *J* = 8.5 Hz, 4H) 4.94 (s, 1H); 2.71 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.77 (d, *J* = 243.8 Hz), 140.16 (d, *J* = 2.5 Hz), 128.69 (d, *J* = 8.75 Hz), 115.23 (d, *J*=21.25Hz), 62.86, 46.07, 23.15; HR-MS (ESI): Calculated for $C_{16}H_{18}F_2N$ [M+H]: 262.1402, Found :262.1402; ^{19}F NMR (300 MHz, $CDCl_3$) δ -116.37

Compound **1l**: 94% yield (1.85 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 4.82 (s, 1H), 2.42 (d, *J* = 7.0 Hz, 2H), 1.80 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 144.51, 128.41, 127.29, 126.87, 67.65, 56.26, 28.63, 20.74; HR-MS (ESI): Calculated for $C_{17}H_{22}N$ [M+H]: 240.1746, Found: 240.1747

Compound **1m**: 83% yield (1.9 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.43 (d, *J* = 7.5 Hz, 4H), 7.31 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 4.81 (s, 1H), 1.89 (s, 1H), 1.79-1.82 (d, 2H), 1.64-1.76 (m, 3H), 1.46-1.56 (m, 1H), 1.12-1.32 (m, 3H), 0.89-0.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 144.40, 128.41, 127.30, 126.88, 67.67, 54.98, 37.24, 31.50, 26.73, 26.11; HR-MS (ESI): Calculated for $C_{20}H_{26}N$ [M+H]: 280.2060, Found: 280.2060

Compound **1p**: 86% yield (1.95 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.5, 3.0 Hz, 4H), 6.98 (t, *J* = 9.0 Hz, 4H), 4.75(s, 1H), 2.35 (d, *J* = 7.0 Hz, 2H), 0.92 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 161.80 (d, *J* = 243.7 Hz), 140.06 (d, *J* = 3.8 Hz) 128.59 (d, *J* = 8.75 Hz) 115.24(d, *J* = 21.2 Hz) 66.19, 56.09, 28.60, 20.67; HR-MS (ESI): Calculated for $C_{17}H_{19}F_2N$ [M+H]: 276.1558, Found: 276.1558; ^{19}F NMR (300MHz, $CDCl_3$) *δ* -116.29

Compound **1q**: 90% yield (2.3 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 4H), 7.26 (d, *J* = 8.5 Hz, 4H), 4.73(s, 1H), 2.35 (d, *J*=6.5Hz, 2H), 1.74 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 142.57, 132.74, 128.66, 128.48, 128.47, 66.35, 56.07, 28.61, 20.66; HR-MS (ESI): Calculated for $C_{17}H_{20}Cl_2N$ [M+H]: 308.0966, Found: 308.0967

Compound **1n**: 94% yield; light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.69(s, 2H), 7.58 (d, *J* = 5.0 Hz, 2H), 7.49 (d, *J* = 5.0 Hz, 2H), 7.43 (t, *J* = 5.0 Hz, 2H), 4.89 (s, 1H), 2.37 (d, *J* = 10.0 Hz, 2H), 1.76 (m, 1H), 0.94 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 144.65, 130.9 (d, *J* = 32.5 Hz), 130.6 (d, *J* = 1.3 Hz), 129.1, 124.1 (d, *J* = 27.0 Hz), 124.2 (d, *J* = 3.8 Hz), 123.9 (d, *J* = 3.8 Hz), 123.0, 67.0, 56.1, 28.6, 20.6; HR-MS (ESI): Calculated for $C_{19}H_{20}F_6N$ [M+H]: 376.1493, Found: 376.1494; ^{19}F NMR (300 MHz, $CDCl_3$) δ -62.91

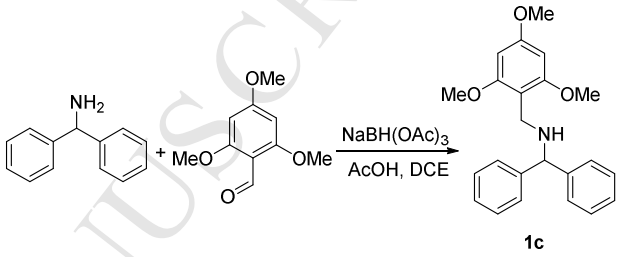
Compound **1o**: 88% yield; light oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.25 (m, 6H), 7.03 (d, *J* = 10.0 Hz, 2H), 4.73(s, 1H), 2.40 (d, *J* = 5.0 Hz, 2H), 2.34 (s, 6H), 1.80 (m, 1H), 0.94 (d, *J* = 10.0 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.49, 137.93, 128.27, 128.26, 127.97, 127.61, 124.30, 67.62, 56.30, 28.55, 21.51, 20.75; HR-MS (ESI): Calculated for $C_{19}H_{26}N$ [M+H]: 268.2059, Found: 268.2060

Compound **1r**: 90% yield; light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.5 Hz, 4H), 7.53 (d, *J* = 8.5 Hz, 4H), 4.89 (s, 1H), 2.37 (d, *J* = 6.5 Hz, 2H), 1.77 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.58, 129.56 (q, *J* = 32.5 Hz), 127.49, 125.59 (q, *J* = 3.8 Hz), 124.06 (q, *J* = 270 Hz), 67.01, 56.08, 28.65, 20.61; ^{19}F NMR (300 MHz, $CDCl_3$) δ -62.86; HR-MS (ESI): Calculated for $C_{19}H_{20}F_6N$ [M+H]: 376.1495, Found: 376.1494

Compound **1s**: 93% yield; light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 10.0 Hz, 4H), 7.12 (d, *J* = 10.0 Hz, 4H) 4.76 (s, 1H), 2.41 (d, *J* = 10.0 Hz, 2H), 2.32 (s, 6H), 1.79 (m, 1H), 0.94 (d, *J* = 10.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.19, 136.32, 129.10, 127.10, 67.03, 56.26, 28.61, 21.07, 20.76; HR-MS (ESI): Calculated for $C_{19}H_{26}N$ [M+H]: 268.2058, Found: 268.2060

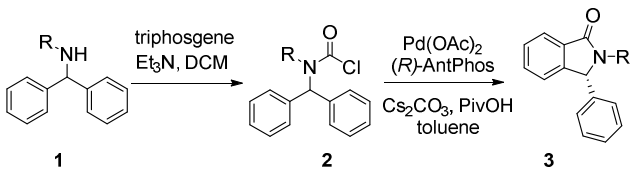
Compound **1t**: 78% yield; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 25, 7.5 Hz, 8H), 4.75 (s, 1H), 2.39 (d, *J* = 7.0 Hz, 2H), 1.78 (m, 1H), 1.29 (s, 18H), 0.92 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.48, 141.50, 126.87, 125.24, 67.00, 56.27, 34.39, 31.38, 28.55, 20.75; HR-MS (ESI): Calculated for $C_{25}H_{38}N$ [M+H]: 352.2996, Found: 352.2999

4.3.2 Synthesis of compound 1c



To a mixture of diphenylmethylamine (1.0 g, 5.45 mmol 1.0 equiv) and 2,4,6-trimethoxybenzaldehyde (1.07 g 5.45 mmol, 1.0 equiv) in dichloroethane (20 mL) at rt was added $NaBH(OAc)_3$ (2.3 g, 10.85 mmol, 2.0 equiv) followed by dropwise addition of AcOH (0.62 mL, 10.85 mmol, 2.0 equiv). The mixture was stirred until the starting material disappeared completely by TLC. Water (30 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with dichloroethane (20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to provide product **1c** as white solid. Compound **1c**: 94% Yield; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.44 (d, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.5 Hz, 2H), 6.14(s, 2H), 4.82(s, 1H), 3.84(s, 3H), 3.79(s, 2H), 3.75(s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 160.32, 159.48, 144.65, 128.20, 127.55, 126.67, 109.30, 90.42, 66.34, 55.52, 55.34, 39.84; HR-MS (ESI): Calculated for $C_{23}H_{26}NO_3$ [M+H]: 364.1906, Found: 364.1907

4.3.3 General procedures for carbamoyl chloride formation and enantioselective palladium-catalyzed cyclization



To a solution of amine **1** (0.2 mmol, 1.0 equiv) and trimethylamine (0.086 mL, 3.0 equiv) in dichloroethane (2.0 mL) at 0 ℃ was added dropwise a solution of triphosgene solution (0.2 mmol in 2 mL DCM). The mixture was allowed

to warm to rt and stirred for 6 h. Saturated sodium bicarbonate solution (20 mL) was added to quench this reaction. The organic layer was separated and the aqueous phase was extracted with dichloroethane for 3 times (2 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was used directly for the next step without any further purification. To the mixture of $Pd(OAc)_2$ (0.4 mg, 1 mol %), (*R*)-AntPhos (3.0 mg, 4 mol %), PivOH (7.0 mg, 30 mol %), Cs_2CO_3 (66 mg, 1.0 equiv) and substrate **2** (~0.2 mmol) was added toluene (2 mL) in the glove box. The mixture was then transferred to an autoclave and charged with CO pressure (9 atm). The mixture was stirred at 80 □ for 24 h. Water (2 mL) was added to the mixture to quench the reaction. The organic layer was separated and the aqueous phase was extracted with EtOAc (2 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to give product **3**, whose enatiomeric excess was determined by chiral HPLC.

Product **3a**: 91% yield; ee 79%; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.9 (m, 1H), 7.42-7.47 (m, 2H), 7.20-7.40 (m, 3H), 7.10-7.20 (m, 3H), 5.34 (s, 1H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.70, 146.03, 136.96, 131.64, 129.13, 128.64, 128.44, 128.42, 128.28, 127.39, 123.43, 122.93, 66.60, 27.49; MS (ESI): [M+H$^+$] found: 224.05; HR-MS (ESI): calculated for $C_{15}H_{13}NO$ [M+H]: 224.1070, found: 224.1074; $[\alpha]_D^{25}$ = -61.04 (c = 1, $CHCl_3$).

Product **3b**: 90% yield; ee 94%; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (m, 1H), 7.42 (m, 2H), 7.32 (m, 3H), 7.19 (m, 2H), 7.07 (m, 1H), 5.48 (s, 1H), 1.35 (d, *J* = 10.0 Hz, 3H), 1.03 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.81, 146.79, 138.82, 131.93, 131.59, 128.82, 128.42, 128.14, 127.69, 123.26, 122.87, 63.83, 45.22, 21.24, 20.58; MS (ESI): [M+H$^+$] found: 252.10; HR-MS (ESI): calculated for $C_{17}H_{17}NO$ [M+H]: 252.1383, found: 252.1387;$[\alpha]_D^{25}$ = -54.88 (c = 1, $CHCl_3$).

Product **3e:** 57% yield; 93% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.86-7.91 (m, 1H), 7.42-7.48 (m, 3H), 7.10-7.20 (m, 3H), 5.44 (s, 1H), 3.92 (m, 1H), 2.85 (m, 1H), 1.53 (m, 2H), 1.27 (m, 4H), 0.84 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.53, 146.22, 137.15, 131.56, 129.05, 128.58, 128.23, 127.53, 123.49, 122.97, 64.38, 40.13, 28.97, 27.91, 22.31, 13.90; MS (ESI): [M+H$^+$] 280.00; HR-MS (ESI): calculated for $C_{19}H_{21}NO$ [M+H]: 280.1696, found: 280.1696; $[\alpha]_D^{25}$ = -51.97 (c = 1, $CHCl_3$)

Product **3f:** 74% yield; 99% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.90 (m, 1H), 7.40-7.50 (m, 2H), 7.26-7.32 (m, 3H), 7.10-7.18 (m, 2H), 7.03-7.08 (m, 1H), 5.41 (s, 1H), 3.82-3.91 (m, 1H), 1.68-1.84 (m, 2H), 1.85-1.30 (m, 2H), 0.74-0.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.43, 146.21, 137.12, 131.78, 131.55, 129.05, 128.60, 128.23, 127.56, 123.46, 122.97, 64.30, 38.45, 37.02, 25.82, 22.65, 22.20; MS (ESI): [M+H$^+$] 280.05; HR-MS (ESI): calculated for $C_{19}H_{21}NO$ [M+H]: 280.1694, found: 280.1696; $[\alpha]_D^{25}$ = -62.38 (c = 1, $CHCl_3$)

Product **3g**: 80% yield; 94% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.86 (m, 1H), 7.39-7.44 (m, 2H), 7.30-7.36 (m, 3H), 7.18-7.22 (m, 2H), 7.09-7.13 (m, 1H), 5.56 (s, 1H), 4.5 (m, 1H), 2.50 (m, 1H), 2.23(m, 1H), 2.12 (m, 1H), 1.90 (m, 1H), 1.55-1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.98, 146.53, 138.81, 131.67, 129.01, 128.31, 128.17, 126.96, 123.40, 122.80, 109.99, 64.26, 48.17, 29.10, 28.44, 15.73; MS (ESI): [M+H$^+$] 264.00; HR-MS (ESI): calculated for $C_{19}H_{21}NO$ [M+H]: 264.1382, found: 264.1383; $[\alpha]_D^{25}$ = -22.95 (c = 0.5, $CHCl_3$)

Product **3h**: 88% yield; 91% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.87 (t, *J* = 5.0 Hz 1H), 7.39-7.44 (m, 2H), 7.29-7.34 (m, 3H), 7.17-7.21 (d, *J* = 10.0 Hz, 2H), 7.06-7.10 (t, *J* = 5.0 Hz, 1H), 5.49 (s, 1H), 4.20 (m, 1H), 1.98 (m, 1H), 1.80-1.89 (m, 1H), 1.71-1.76 (m, 1H), 1.41-1.64 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 169.11, 146.67, 138.81, 131.95, 131.54, 128.91, 128.35, 128.11, 127.27, 123.20, 122.81, 64.96, 55.24, 29.81, 29.39, 23.91, 23.68; MS (ESI): [M+H$^+$] 278.00; HR-MS (ESI): calculated for $C_{19}H_{19}NO$ [M+H]: 278.1538, found: 278.1539; $[\alpha]_D^{25}$ = -127.76 (c = 1, $CHCl_3$)

Product **3i**: 94% yield; 95% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.84-7.88 (m, 1H), 7.41 (m, 2H), 7.30-7.34 (m, 3H), 7.16-7.20 (m, 2H), 7.03-7.06 (m, 1H), 5.49 (s, 1H), 3.94-4.02 (m, 1H), 1.74-1.85 (m, 3H), 1.51-1.64 (m, 3H), 1.21-1.32 (m, 2H), 1.06-1.17 (m, 1H), 0.93-1.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.85, 146.93, 139.00, 131.76, 131.55, 128.77, 128.35, 128.08, 127.58, 123.31, 122.86, 63.86, 53.41, 31.58, 31.10, 26.06, 25.93, 25.36; MS (ESI): [M+H$^+$] 292.20; HR-MS (ESI): calculated for $C_{20}H_{21}NO$ [M+H]: 292.1694, found: 292.1696; $[\alpha]_D^{25}$ = -130.69 (c = 1, $CHCl_3$)

Product **3j**: 77% yield; 99% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.85-7.90 (m, 1H), 7.41-7.47 (m, 2H), 7.27-7.33 (m, 3H), 7.11-7.17 (m, 2H), 7.03-7.08 (m, 1H), 5.41 (s, 1H), 3.84 (m, 1H), 1.67-1.86 (m, 2H), 1.17-1.30 (m, 2H), 0.730-0.815 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 169.57, 146.72, 138.56, 131.95, 131.62, 128.64, 128.56, 128.33, 128.18, 123.35, 123.01, 64.11, 57.38, 26.32, 25.93, 11.48, 11.39; MS (ESI): [M+H$^+$] 280.45; HR-MS (ESI): calculated for $C_{19}H_{21}NO$ [M+H]: 280.1695 found: 280.1696; $[\alpha]_D^{25}$ = -36.50 (c = 1, $CHCl_3$)

Product **3k**: 74% yield; 96% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 10.0, 5.0 Hz, 1H), 7.10-7.20 (m, 3H), 6.95-7.05 (m, 3H), 5.45 (s, 1H), 4.29 (m, 1H), 1.33 (d, *J* = 5.0 Hz, 3H) 1.03 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 167.49 (d, *J* = 2.5 Hz), 163.83 (d, *J* = 26.3 Hz), 161.9 (d, *J* = 25.0 Hz), 141.99, 134.16 (d, *J* = 2.5 Hz), 134.0 (d, *J* = 8.8 Hz), 129.3 (d, *J* = 8.8 Hz), 124.4 (d, *J* = 8.8 Hz), 119.3 (d, *J* = 23.8 Hz), 115.98 (d, *J* = 21.3 Hz), 110.02 (d, *J* = 22.5 Hz), 62.72, 45.45, 21.16, 20.55; MS (ESI): $[M+H^+]$ 288.05; HR-MS (ESI): calculated for $C_{17}H_{15}F_2NO$ [M+H]: 288.1193, found: 288.1194; ^{19}F NMR (300 MHz, $CDCl_3$): δ-113.25; $[\alpha]_D^{25}$ = -38.97 (c = 1, $CHCl_3$)

Product **3l**: 98% yield; 99% ee; white solid; Chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.90 (m, 1H), 7.45 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.31-7.37 (m, 3H), 7.14-7.18 (m, 1H), 7.1-7.13 (m, 2H), 3.73 (dd, *J* = 15.0, 10.0 Hz, 1H) 2.66 (dd, *J* = 15.0, 10.0 Hz, 1H); 1.88-1.99 (m, 1H) 0.89 (dd, *J* = 15.0, 10.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.86, 146.24, 137.7, 131.62, 129.08, 128.60, 128.25, 127.55, 123.61, 122.96, 64.78, 47.45, 27.57, 20.40, 19.86; MS (ESI): $[M+H^+]$ 266.15; HR-MS (ESI): calculated for $C_{18}H_{19}NO$ [M+H]: 266.1538, found: 266.1539; $[\alpha]_D^{25}$ = -109.92 (c = 1, $CHCl_3$)

Product **3m**: 87% yield; 96% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm. ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.80-7.90 (m, 1H), 7.42-7.47 (m, 2H), 7.30-7.37 (m, 3H), 7.14-7.17 (m, 1H), 7.10-7.13 (m, 2H), 5.45 (s, 1H), 3.78 (dd, *J* =15.0, 10.0 Hz, 1H), 2.66 (dd, *J* = 15.0, 10.0 Hz, 1H), 1.57-1.67 (m, 6H), 1.10-1.20 (m, 3H), 0.92-1.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.86, 146.23, 137.13, 131.62, 131.58, 129.06, 128.58, 128.23, 127.55, 123.58, 122.95, 64.99, 46.26, 36.89, 31.08, 30.52, 26.33, 25.81, 25.70; MS (ESI): $[M+H^+]$ 306.40; HR-MS (ESI): calculated for $C_{21}H_{23}NO$ [M+H]: 306.1851, found: 306.1852; $[\alpha]_D^{25}$ = -94.39 (c = 1, $CHCl_3$)

Product **3c**: 61% yield, 96% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm. ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 10.0 Hz, 1H), 7.33-7.41 (m, 2H); 7.22-7.28 (m, 3H), 7.03 (d, *J* = 5.0 Hz, 1H), 7.0 (m, 2H), 6.0 (s, 2H), 5.16 (s, 0.5H), 5.13 (s, 1H), 4.27 (d, 15.0 Hz, 1H), 3.79 (s, 3H), 3.57 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.32, 161.06, 159.74, 146.74, 138.26, 131.26, 131.17, 128.39, 127.79, 127.66, 126.97, 123.42, 122.74, 104.95, 89.91, 63.91, 55.37, 55.28, 33.07; MS (ESI): $[M+H^+]$ 390.20; HR-MS (ESI): calculated for $C_{24}H_{23}NO_4$ [M+H] 390.1705, found: 90.1703; $[\alpha]_D^{25}$ = -26.44 (c = 1, $CHCl_3$)

Product **3n**: 72% yield; 75% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 10.0 Hz, 1H), 7.77 (d, *J* = 5.0 Hz, 1H), 7.66(d, *J* = 10.0 Hz, 1H), 7.53 (t, *J* = 10.0 Hz, 1H), 7.42 (d, *J* = 5.0 Hz, 2H), 7.29 (d, *J* = 10.0 Hz, 1H), 5.57 (s, 1H), 3.77 (dd, *J* = 15.0, 5.0 Hz, 1H), 2.65 (dd, *J* = 15.0, 10.0 Hz, 1H), 1.92 (m, 1H), 0.90 (dd, *J* = 20.0, 10.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.32, 145.68, 137.26, 133.95 (dd, *J* = 64.5, 31.5 Hz), 131.93 (dd, *J* = 64.5, 33.0 Hz), 130.75, 130.11, 129.37, 126.14 (dd, *J* = 6.0, 3.0 Hz), 124.57, 124.51 (d, *J* = 7.5 Hz), 124.48, 122.70(d, *J* = 7.5Hz), 120.22 (d, *J* = 4.5 Hz), 64.22, 47.76, 27.57, 20.34, 19.81; MS（ESI）: $[M+H^+]$ 402.10; HR-MS (ESI): calculated for $C_{20}H_{17}F_6NO$ [M+H]: 402.1284, found: 402.1287 $[\alpha]_D^{25}$ = -50.45 (c = 1, $CHCl_3$)

Product **3o**: 84% yield, 89% ee; white solid; chiral HPLC conditions: Chiralpak IB, 20 ℃, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^1H NMR (500 MHz, $CDCl_3$) δ7.77 (d, *J* = 10.0 Hz, 1H), 7.24 (t, *J* = 10.0 Hz, 2H), 7.13 (d, *J* = 5.0 Hz, 1H), 6.93-6.97 (m, 2H), 6.87 (s, 1H), 5.36 (s, 1H), 3.73 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.64 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 1.87-1.97 (m, 1H), 0.88 (dd, *J* = 10.0 Hz, 5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.97, 146.71, 142.21, 138.87, 137.19, 129.31, 129.21, 129.01, 128.87, 127.88, 124.72, 123.40, 123.34, 64.53, 47.33, 27.55, 21.84, 21.41, 20.41, 19.85; MS (ESI): $[M+H^+]$ 294.45; HR-MS (ESI): calculated for $C_{20}H_{23}NO$ [M+H]: 294.1853, found: 294.1855 $[\alpha]_D^{25}$ = -43.85 (c = 1, $CHCl_3$)

Product **3p**: 83% yield; 95% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 ℃, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^1H NMR (500 MHz, $CDCl_3$) δ7.55 (dd, *J* = 10.0, 5.0 Hz, 1H); 7.16 (td, *J* =10.0, 5.0 Hz, 1H), 7.00-7.13 (m, 5H), 5.41 (s, 1H), 3.70(dd, *J* = 10.0, 5.0 Hz, 1H), 2.63 (dd, *J* = 10.0, 5.0 Hz, 1H), 1.90 (m, 1H), 0.88 (dd, *J* = 10.0, 5.0 Hz, 6H); ^{13}C NMR (125 MHz , $CDCl_3$) *δ* 167.53 (d, *J* = 3.8 Hz), 163.92 (d, *J* = 20.0 Hz), 161.90 (d, *J* = 21.3 Hz), 141.45 (d, *J* = 1.3 Hz), 133.72 (d, *J* = 8.8 Hz), 132.5 (d, *J* = 2.5 Hz), 129.24 (d, *J* = 7.5 Hz), 124.51 (d, *J* = 8.8 Hz) 119.25 (d, *J* = 23.8 Hz), 116.22 (d, *J* = 21.3 Hz), 110.39 (d, *J* = 23.8 Hz), 63.68, 47.62 , 27.56 , 20.35, 19.82; MS (ESI): $[M+H^+]$ 302.05; HR-MS (ESI): calculated for $C_{18}H_{17}F_2NO$ [M+H]: 302.1349, found: 302.1351; ^{19}F NMR (300MHz, $CDCl_3$): δ -113.00; $[\alpha]_D^{25}$ = -72.78 (c = 1, $CHCl_3$)

Product **3q**: 91% yield; 92% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 ℃, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.5 Hz, 1H), 7.43 (dd, *J* = 10.0, 2.5 Hz, 1H), 7.33 (d, *J* = 10.0 Hz, 2H), 7.07 (d, *J* = 10.0 Hz, 1H), 7.04 (d, *J* = 10.0 Hz, 2H), 5.40 (s, 1H), 3.70 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.63 (dd, *J* = 15.0, 5.0 Hz, 1H), 1.84-1.94 (m, 1H), 0.88 (dd, *J* = 15.0, 5.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.33, 143.88, 135.05, 134.88, 134.81, 133.33, 131.95, 129.49, 128.84, 124.20, 123.90, 63.76, 47.62, 27.54, 20.35, 19.81; MS (ESI): $[M+H^+]$ 334.20; HR-MS (ESI): calculated for $C_{18}H_{17}Cl_2NO$ [M+H]: 334.0759, found :334.0760; $[\alpha]_D^{25}$ = -74.69 (c = 1, $CHCl_3$)

Product **3r**: 73% yield; 92% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 ℃, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^1H NMR (500 MHz, $CDCl_3$ *δ* 8.19(s, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.65 (d, *J* = 10.0 Hz, 2H), 7.28 (t, *J* = 5.0 Hz, 3H), 5.58 (s, 1H), 3.79 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.66 (dd, *J* = 15.0, 5.0 Hz, 1H), 1.88-1.98 (m, 1H), 0.9 (dd, 15.0, 5.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.35, 148.50, 140.24, 132.30, 131.51(dd, *J* = 88.5, 55.5Hz), 131.50 (dd, *J* = 42.0, 9.0 Hz) , 128.8 (dd, *J* =7.5, 3.0 Hz), 127.88, 126.44 (dd, *J* = 7.5, 4.5 Hz), 124.59 (d, *J* = 4.5 Hz), 123.67, 122.78 (d, *J* = 4.5 Hz), 121.34 (dd, *J* = 7.5, 4.5 Hz), 64.13, 47.73, 27.58, 20.37, 19.82; MS (ESI): $[M+H^+]$ 402.15; HR-MS (ESI): calculated for $C_{20}H_{17}F_6NO$ [M+H]: 402.1284, found: 402.1287; $[\alpha]_D^{25}$ = -74.41 (c = 1, $CHCl_3$)

Product **3s**: 91% yield; 95% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.25 (m, 1H), 7.14 (d, *J* = 5.0 Hz, 2H), 7.04 (d, *J* = 5.0 Hz, 1H), 6.98 (d, *J* = 10.0 Hz, 2H), 5.38 (s, 1H), 3.71 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.64 (dd, *J* = 15.0, 5.0 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H), 1.87-1.97 (m, 1H), 0.88 (dd, *J* = 10.0, 5.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.92, 143.78, 138.32, 138.20, 134.25, 132.56, 131.77, 129.70, 127.44, 123.74, 122.64, 64.33, 47.37, 27.57, 21.31, 21.15, 20.40, 19.85; MS (ESI): [M+H$^+$] 294.40; HR-MS (ESI): Calculated for $C_{20}H_{23}NO$ [M+H]: 294.1851, found :294.1852; $[\alpha]_D^{25}$ = -71.68 (c = 1, $CHCl_3$)

Product **3t**: 91% yield; 96% ee; white solid; chiral HPLC conditions: Chiralpak AD-H, 20 □, flow rate: 0.7 mL/min, hexanes/isopropanol: 80/20, 254 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 5.0 Hz, 1H), 7.48 (dd, *J* = 10.0, 5.0 Hz, 1H), 7.34 (d, *J* = 10.0 Hz, 2H), 7.10 (d, *J* = 10.0 Hz, 1H), 7.03 (d, *J* = 10.0 Hz, 2H), 5.40 (s, 1H), 3.75 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.66(dd, *J* = 15.0, 5.0 Hz), 1.90-1.99 (m, 1H), 1.35(s, 9H), 1.30 (s, 9H), 0.89 (dd, *J* = 10.0, 5.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.23, 151.62, 151.39, 143.69, 134.09, 131.43, 128.94, 127.10, 125.90, 122.47, 120.25, 64.15, 47.35, 34.97, 34.58, 31.44, 31.28, 27.60, 20.43, 19.87; MS (ESI): [M+H$^+$] 378.20; HR-MS(ESI): calculated for $C_{26}H_{35}NO$ [M+H]: 378.2791, found: 378.2891; $[\alpha]_D^{25}$ = -53.88 (c = 1, $CHCl_3$)

Acknowledgements

We are grateful to the Strategic Priority Research Program of the Chinese Academy of Sciences XDB20000000, CAS (QYZDY-SSW-SLH029), NSFC-(21725205, 21432007, 21572246, 21702223), and K.C.Wong Education Foundation.

Supplementary data

Supplementary data associated with this article can be found in the online version.

Notes and references

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